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Occurrence of Neonicotinoids in Chinese Apiculture and its Risk Exposure Assessment

Xinran Wang[a], Dave oulson [b], Lanzhen Chen[a,c,d,e], Jinzhen Zhang[a,c,d,e], Wen Zhao[a,c,d,e], Yue Jin[a,c,d,e], Shupeng Yang[a,c,d,e*], Yi Li[a,c,d,e*], Jinhui Zhou[a,c,d,e*]

[a] *Institute of Apicultural Research, Chinese Academy of Agricultural Sciences, Beijing 100093, PR China*

[b] *School of Life Sciences, University of Sussex, Brighton BN1 9Q, United Kingdom*

[c] *Laboratory of Risk Assessment for Quality and Safety of Bee Products, Ministry of Agriculture, Beijing 100093, PR China*

[d] *Key Laboratory of Bee Products for Quality and Safety Control, Ministry of Agriculture, Beijing 100093, PR China*

[e] *Bee Product Quality Supervision and Testing Centre, Ministry of Agriculture, Beijing 100093, PR China*

Corresponding author. Tel: 86-10-6259-6429; Fax: 86-10-6259-4643; Email: zhoujinhui@caas.cn (Jinhui Zhou). Shupeng Yang, Yi Li and Jinhui Zhou contributed equally to this work.

Abstract

Neonicotinoids are the most widely used insecticides in the world, but there is mounting evidence demonstrating that they have adverse effects on non-target organisms. However, little is known about the extent of environmental contamination with neonicotinoids in China. In this study, a total of 693 honey samples from across China, from both *Apis melifera* and *Apis cerana,* were analyzed to examine neonicotinoid concentrations, geographical distribution, and the primary plant species from which the honey was obtained. Further, chronic and acute exposure risk and risk ranking for humans eating honey were investigated, and also risks to bees were considered. The results revealed that 40.8% of the samples contained at least one of five neonicotinoids tested. Honeys from commercial crops were found to be more frequently contaminated with neonicotinoids than those from non-commercial crops. Honey from *Apis mellifera* was more frequently contaminated than honey from *Apis cerana*. Concentrations of neonicotinoids found in honey overlap with those that have been found to have significant adverse effects on honeybee health. The dietary risk assessments indicated that levels of neonicotinoids in honey were likely to be safe for human consumption.

Keywords: Neonicotinoid pesticides; Chinese honey; Entomological and floral origins; eographical distribution; Dietary intake risk

1. Introduction

In recent years, neonicotinoid pesticides have been causing widespread concern worldwide due to growing evidence that they have adverse effects on honey bees[1, 2]. The neonicotinoid family of pesticides is a class of neuroactive compounds including imidacloprid (IMI), acetamiprid (ACE), thiacloprid (THP), thiamethoxam (THM), clothianidin (CLO), nitenpyram (NIT) and dinotefuran (DIN) [3]. They are often directly sprayed on the crop, with a risk of them blowing in the wind to contaminate nectar and pollen of nectariferous plants nearby. In addition, with the increasing prevalence of industrial farming, neonicotinoid pesticides have been progressively accumulating in the soil and water due to their use as soil treatments, foliar applications and seed coatings over the past several years, and, as a result, they may be further transferred to nectar and pollen of nectariferous plants via root uptake[4].

Recent studies have reported that neonicotinoid pesticides have serious negative effects on the behavior and function of honey bees, including impairing olfaction and taste, [5, 6] foraging and homing ability, [7-9] immune function,[10, 11] and memory.[12, 13] IMI, CLO and THM were completely banned for outdoor use by the European Commission on December 19, 2018 due to increasing concern about the reported environmental harm caused by neonicotinoids. In addition, France has taken the lead in banning the use of all five neonicotinoids that were previously allowed in Europe (CLO, IMI, THM, THP and ACE) in both outdoors and greenhouses from September 1, 2018. Following international regulations on pesticide administration that have popularized the use of low-toxic and low-residue insecticides, the use of insecticides will reach zero growth by 2020 as required by Ministry of Agriculture in China.[12]

While the risk posed to bees has received much attention, the risk posed by neonicotinoids to

humans via consumption of honey is not clear. With the aim of protecting the health of human from the adverse effects of exposure to neonicotinoid pesticides, maximum residue levels (MRLs) of these pesticides in honey have been established in the European union (EU), ranging from 50-200 μg/kg. [13]

A survey of neonicotinoids in 198 honey samples from across the world reported in 2017 found that 75% of all samples contained at least one neonicotinoid, 45% contained two or more pesticides, and 10% contained four or five pesticides.[14] It is well known that China is the largest beekeeping country in the world, with 9 million colonies of honey bees, which accounts for one-ninth of the total honey bee colonies worldwide.[15] In addition, China is the largest honey producer and exporter in the world, with about 25% of the honey on the international market coming from China[16]. Thus, the presence of neonicotinoid insecticides in Chinese apiculture has the potential to have a major impact on apiculture worldwide.

In this study, we collected honey samples from the main honey producing areas of China，measured the concentration of five neonicotinoid pesticides (IMI, ACE, THP, THM and CLO), which were the most frequently used in China, and plotted the geographic distribution of neonicotinoid pesticides in honey. Then, the relationship between neonicotinoid levels and geographical locality, floral origin and entomological origins was analyzed. Finally, we assessed the exposure risk of the five neonicotinoids in honey to human and bees.

2. Method and Materials

2.1. Sample collection.

A total of 693 honey samples were collected in 2018 from the main honey producing areas of 19 provinces which covered all 7 geographical regions of China, varying from subarctic to subtropical

88 climates. A geographic information system (GIS, ArcGIS 9.3; ESRI Japan) was used to visualize the
89 location of each sample in China (Fig.1). The magnified view of the sampling location for each
90 province is shown in Fig. S1-13, except Inner Mongolia, Shandong, Ningxia, Yunnan, Guangxi and
91 Fujian Province, in which the sample information could be represented clearly in Fig.1. All the main
92 floral origins of honey in China were included in this study. The detailed information of each sample
93 was shown in Table S1. Care was taken to avoid the contamination from equipment, sampling and
94 sample preparation procedures by using new glassware and equipment that was pre-washed to
95 keep them clean, then subjected to check for contamination by analyzing solvent blanks both prior
96 to sample injection and post injection. In order to guarantee the authenticity of the honey, all
97 samples were obtained from different apiaries by researchers and beekeepers together. All honey
98 samples were stored in the dark at 4 ℃ before analysis. If the honey crystallized prior to analysis, it
99 was placed in a 40 ℃ water bath to ensure its homogeneity.

100 **2.2. Reagents and chemicals.**

101 The neonicotinoids IMI, ACE, THP, THM, CLO were obtained from Aladdin (Shanghai, China). Stock
102 solutions (1,000 μg/mL) of each neonicotinoid were prepared in methanol. Also, a mixed working
103 standard solution of 1 μg/mL was prepared in acetonitrile. All the solutions were stored at 4 ℃.
104 Ultrapure water was prepared by using a Milli-Q Plus device from Millipore (Bedford, MA, USA).
105 Formic acid, acetonitrile and methanol were obtained from Fisher Chemicals (Fair Lawn, NJ, USA).
106 Sodium chloride, anhydrous magnesium sulfate, and primary secondary amine (PSA) were provided
107 by Shimadzu Corp. (Kyoto, Japan).

108 **2.3. Apparatus and LC–MS/MS conditions.**

109 The Agilent 1200 HPLC system used in this study consisted of a binary pump, an autosampler, a

column compartment and a vacuum degasser. Chromatographic separation was performed using a Phenomenex Kinetex C18 column (50×2.1 mm, 2.6 μm) at 35 °C. The mobile phase consisted of 0.1% formic acid in water and acetonitrile. The linear gradient elution was as follows (in% B): 0 min, 10%; 0.5 min, 10%; 1 min, 50%; 7 min, 50%; 7.1 min, 10%; 9 min, 10%. The flow of the mobile-phase was set at 0.4 mL/min with an injection volume of 5 μL.

An Agilent 6460 triple quadrupole tandem mass spectrometer coupled with an Agilent Jet Stream equipped with electrospray ionization (AJS-ESI) ion source (Agilent Technologies, Santa Clara, CA, USA) was used in this experiment. The system operation, data acquisition, and analysis were controlled by the MassHunter Acquisition software (Agilent Technologies). The analysis in the MS/MS system was conducted by multiple reaction monitoring (MRM) in the positive ionization mode. The following instrument conditions were used: capillary voltage, 3.5 kV; sheath gas temperature, 250 °C; sheath gas flow, 12 L/min; drying gas temperature, 300 °C; drying gas flow, 5 L/min; nebulizer, 45 psi; cone voltage, 0 V. The transitions of the compounds and the cracking voltage and collision energy are summarized in Table S2.

2.4. Sample preparation.

Two grams of honey were added into a 50-mL polypropylene centrifuge tube containing 10 mL of water. The mixture was vortexed until the honey sample was completely dissolved. Then 10 mL of acetonitrile with extraction salt (4 g $MgSO_4$, 1 g NaCl) was added to the honey/water solution and vortexed to mix completely. Then, the mixture was centrifuged for 10 min at 8,800 rpm and at 4 °C. Afterwards, 5 mL of the upper solution was transferred into a 10-mL polypropylene centrifuge tube containing the purification salts (150 mg $MgSO_4$, 60 mg PSA). Then, the tube containing the mixture was centrifuged for 10 min at 8,800 rpm and at 4 °C. The upper layer was taken out and evaporated

to dryness at 40 ℃. The residues were dissolved in 1 mL acetonitrile and filtered through 0.22 μm nylon membrane before analysis by LC–MS/MS.

2.5. Method validation.

The method described in this paper was validated following SANCO/12571/2013[17-19]. Blank control samples were prepared and analyzed to verify the cleanliness of the HPLC-MS/MS system and used to eliminate background interference. Simultaneously, a standard as a quality control (QC) sample was interspersed in the whole sequence to ensure the stability of the system and the accuracy of the analysis. The blank matrix samples were finally selected after sample preparation and detection following established methods[20]. The following parameters were validated to ensure method reliability: limit of detection (LOD), limit of quantification (LOQ), the matrix effect, linearity range, accuracy and precision. For linearity, solvent standard calibration curves and matrix-matched calibration curve of five neonicotinoids was assessed using the correlation between the target peak areas and the matrix-matched standard concentrations at six concentration levels ranging from 0.1-200 ng/ml respectively. The matrix effects were assessed as B/A × 100%, where A and B represented the slopes of the solvent standard and the matrix -matched calibration curves, respectively. The signal-to-noise ratio (SNR) of 3 and 10 was taken to determine LOD and LOQ, respectively. The accuracy was evaluated by calculating the recoveries of spiking blank matrix samples at three levels (LOQ, 2LOQ, 10LOQ) in five replicates. Also, the precision was evaluated by studying intra-day precision and inter-day precision, and these were expressed as relative standard deviations (RSD).

2.6. Dietary exposure risk assessment.

Dietary exposure risk assessment was estimated in terms of chronic exposure, acute exposure and risk ranking, respectively.

154 2.6.1. Chronic dietary exposure assessment.

155 Chronic dietary exposure assessments were performed for neonicotinoids in honey that have
156 adverse health effects from exposure over a long period[21, 22]. National estimated daily intake (NEDI)
157 was used to estimate chronic (long-term) dietary exposure and calculated by equation (1) [25, 26]. In
158 the chronic exposure risk assessment, %ADI was defined as the ratio between NEDI and the
159 acceptable daily intake (ADI).

160 $$\mathrm{NEDI} = \frac{STMR * ADC}{bw} \quad (1)$$

161 $$\%\mathrm{ADI} = \frac{NEDI}{ADI} \quad (2)$$

162 where, STMR is the supervised trials average residue (mg/kg) in this study, ADC denotes the average
163 daily consumption of honey in China (0.01 kg per day),[25] and bw is the average body weight of 60
164 kg.[26]

165 The %ADI represents the chronic exposure risk, and the smaller the %ADI value is, the lower the
166 risk from chronic dietary intake of the pesticide. When the %ADI value is lower than 100, the risk is
167 deemed to be acceptable.

168 2.6.2. Acute dietary exposure assessment.

169 The estimated short-term intake (ESTI, kg) of pesticide residues was applied to represent an
170 estimate of acute dietary exposure by equation (3).[27] And the acute exposure risk assessment was
171 expressed by the 100% of acute reference dose (%ARfD) and calculated by equation (4).

172 $$\mathrm{ESTI} = \frac{LP * HR}{bw} \quad (3)$$

173 $$\%\mathrm{ARfD} = \frac{ESTI}{ARfD} * 100 \quad (4)$$

174 where, LP is the large portion [22], kg (LP=0.1 kg of honey in China),[28] HR denotes the maximum residue
175 level (mg/kg), and bw is the average body weight, kg (bw=60 kg for adults).

176 The acute exposure risk was represented by the %ARfD. According to pesticide risk assessment
177 principles, the smaller the % ARfD is, the lower the risk of chronic dietary intake of the pesticide.
178 When the % ARfD is lower than 100, the risk is deemed to be acceptable.

179 2.6.3. Risk ranking of neonicotinoids in honey.

180 The risk ranking was developed according to the method of the Veterinary Residues Committee
181 of the UK.[29] The indexes included toxicity, potency, dietary proportion, dosing frequency, high
182 exposure population, and residue level, and their values are listed in Table S3. Each neonicotinoids
183 pesticide residues risk score (S) and residue level was calculated using equations (5) and (6),
184 respectively.

185 $$\mathrm{S} = (\mathrm{A} + \mathrm{B}) * (\mathrm{C} + \mathrm{D} + \mathrm{E} + \mathrm{F}) \quad (5)$$

186 $$\mathrm{F} = (F_1 * 1 + F_2 * 2 + F_3 * 3)/\mathrm{N} \quad (6)$$

187 where, A is the toxicity score, B is the score of potency, C is the score of dietary proportion, D is the
188 score of dosing frequency, E is the high exposure population score, F is the residue level score, F_1 is
189 the number of samples that do not exceed the MRL, F_2 is the number of samples with concentration
190 between the MRL and 10MRL, F_3 is the number of samples exceeding the 10MRL, and N is the total
191 number of samples.[30-32]

192 The risk ranking was used to investigate the risk of multiple pesticides in the agricultural
193 products and calculated by combining the toxicity parameters and exposure scores[33]. The toxicity
194 was represented by acute oral toxicity. The half-lethal dose (LD50) and ADI values were acquired
195 from the National Standards, People's Republic of China.[34] According to the LD50, pesticides were
196 classified into 4 classes: extremely high toxicity, high toxicity, mild toxicity and low toxicity.[35] Since
197 there was no standard protocol in China to estimate the population under high exposure, the high

198 exposure group score was set at 3[35]. Based on the average daily consumption of honey and total
199 food intake, honey intake accounted for less than 2.5% of the total diet in China[36]. The toxicity and
200 potency of each pesticide are shown in Table S2 and scores are assigned. Thus, the dietary
201 proportion score is assumed to be 0. When the score is higher than 20, it can be considered a high-
202 risk pesticide; when the score is between 15 and 20, it is a medium risk pesticide; when the score is
203 less than 15, it is a low-risk pesticide.

204 **2.7. Statistical analysis.**

205 Differences of detection rate between regions, between different nectariferous plants,
206 between commercial and non-commercial crops, and between *Apis mellifera* and *Apis cerana* were
207 analyzed by Pearson's Chi-square test. Analyses were performed using SPSS 22.0 (IBM Corporation,
208 New York, USA). Bonferroni corrections for multiple comparisons were applied (α=0.0013 for
209 comparing different region, 0.0006 for comparing different nectariferous plants).

210 **3. Results and discussion**

211 **3.1. Method validation.**

212 Both the solvent standard calibration curves and matrix-matched calibration curve showed
213 acceptable linearity with correlation coefficients (R^2) that were higher than 0.99. The matrix effect
214 produced by the co-elution of the matrix components could enhance or suppress the analyte's
215 signal and generated deviation of quantitative data. It was evaluated by the slope ratio of both the
216 matrix-matched calibration curve and the pure standard solution calibration curve. The matrix effect
217 was considered as an enhancement effect when the slope ratio was higher than 1.2, and a
218 suppression effect when the ratio was lower than 0.8[37]. As shown in Table S4, the matrix effects of
219 five neonicotinoids ranged from 42.14-61.07%, which exhibited a significant suppression effect.

220 Hence, the matrix-matched calibration curve was used to quantify the five neonicotinoid
221 insecticides in honey. Simultaneously, a reconstituted sample was prepared by mixing lychee honey,
222 rape honey, linden honey, chaste honey, jujube honey and acacia honey in the same proportions
223 and was applied to construct a matrix-matched calibration curve to reduce the matrix influence
224 from different samples because different honey samples could generate different matrix effects.
225 The LODs of five pesticides ranged from 0.02-0.08 μg/kg and LOQs were from 0.1-.015 μg/kg. The
226 recoveries of all the neonicotinoids ranged from 71.77-97.32% in three levels were satisfactory for
227 food safety analysis. The RSDs were all lower than 10% for the five pesticides, both in intra-day
228 precision and inter-day precision, fulfilling the criteria of RSD≤20%. Hence, the method met the
229 performance requirements, which was suitable for the routine analysis of neonicotinoid pesticide
230 residues in honey.

231 **3.2. Real samples analysis.**

232 In this study, 693 honey samples were collected from 15 main floral origins in China, and the
233 five neonicotinoid insecticides (ACE, IMI, CLO, THM, THP) in these samples were quantified using
234 the newly developed quantification method.

235 3.2.1. The overall detection concentrations of neonicotinoids in China

236 Considering the detected concentration of the five neonicotinoids in China, the total
237 concentration was 5.76 ng/g on average, and reached a maximum of 233.25 μg/kg over all
238 contaminated samples. There are 4 samples with a total concentration over 50 μg/kg, and 12.03% of
239 the samples had a concentration ranging from 10 to 50 μg/kg However, the concentration varied
240 considerably among regions. From the IS map (Fig.1), t he five provinces with the highest average
241 content of neonicotinoids in their honey were Henan, uangxi, uangdong, Sichuan and ansu. The

242 average neonicotinoid concentration detected in all contaminated samples in these five provinces
243 was between 5.42-23.85 μg/kg, which was far lower than the MRLs. The average concentration of
244 neonicotinoids in the contaminated samples from other provinces ranged from 0.79 to 3.06 μg/kg
245 (Fig. 1).

246 3.2.2. The overall detection rates of neonicotinoids in China

247 As for the total detection rate of all samples, a total of 283 samples were found to contain at
248 least one neonicotinoid either at or above the LOD level. This gives a detection rate of 40.8% in China,
249 lower than the worldwide rate, which was 75% under Mitchell's method[14] and 90% under Chen's
250 method in America[38]. However, the percentage of contaminated samples is inevitably dependent to
251 some extent on the LOD. Thus, we examined Mitchell's raw data and calculated that their detection
252 rate would have been 67.17% with our LOD, which is not significantly different to our value of 40.8%
253 by Pearson's Chi-square test ($X^2 = 3.153$, df =1, P=0.076). Among all the contaminated samples, 67.8%
254 of samples contained a single neonicotinoids, 31.8% of them (90 samples) contained two or three of
255 the neonicotinoids, and only one lychee honey contained four neonicotinoids, while none of the
256 samples contained all five (Fig, 2A).

257 3.2.3. The detection rate and concentration of each neonicotinoid in China

258 ACE had the highest detection rate and IMI had the highest detected concentration (Fig.2B),
259 which it to be expected as ACE and IMI are the commonly used neonicotinoids in Chinese apiculture.
260 The frequency of occurrence was the highest for ACE (160 samples, 23.09%), followed by IMI (146
261 samples, 21.07%), THM (42 samples, 6.20%), THP (32 samples, 4.62%), while that for CLO was the
262 lowest (only 2.74% of samples) (Fig. 2B). The proportion of ACE contaminated samples that
263 were >MRL was 1.9% (3 samples: 146.7, 58.2 and 50.2 μg/kg), 7.0% were in the range 10-50 μg/kg,

and 91.1% were <10μg/kg. The proportion of CLO contaminated samples that were in the range 10-50 μg/kg was 13.3%, 26.7% were in the range 1.0-10 μg/kg, and 60% were below 1.0 μg/kg. The proportion of IMI contaminated samples that were >MRL was 1.4% (2 samples: 88.6 and 85.9 μg/kg), 9.0% were in the range 10-50 μg/kg, and 89.6% were below 10 μg/kg. The concentration of THP and THM in all the contaminated samples was less than 2 and 8 μg/kg, respectively. In addition, as shown in Fig. 2C and Table s5, the average concentration was 5.01, 4.78, 4.36, 1.75 and 0.90 μg/kg, for IMI, ACE, CLO, THM and THP respectively. The residue concentrations of neonicotinoids in over 80% of honey samples were under 10 μg/kg, which is far less than the MRL of EU. According to the MRL set by the EU, the residue concentration of neonicotinoids in 6 samples exceeded the regulated limit and one sample contained two compounds that exceeded the limit.

3.2.4. The difference of detection rates and concentrations of neonicotinoids in honey with different floral origins

The honey samples in this study were collected from 15 of the main kinds of nectariferous plants, including non-commercial plants, such as acacia, chaste, linden, *sapium*, *Vicia villosa* Roth, commercial plants like citrus, jujube, rape, buckwheat, sunflower, chestnut, medlar, longan and lychee, and also wildflowers visited by *Apis cerana*. IMI was detected in all plant species, while ACE was found in all species except buckwheat. From Fig.4, the detection rates of neonicotinoids in honey from different floral origins indicated significant differences ($X^2 = 145.16$, df = 8, $P < 0.001$, Table S9) and were ranked as follows: lychee honey (88.73%)>longan honey (76.19%)>citrus honey (67.65%)>rape honey (49.68%)>acacia honey (43.36%). The detection rate of neonicotinoids in honey from other floral origins was lower than 40%. Also, the majority of contaminated honey samples were harvested early in the year, as was also found by Woodcock et al.[41]. Lychee and longan trees

286 are the major subtropical fruits found in the Southern China region, including uangxi and
287 uangdong , and the highest detection rate of neonicotinoids was in uangxi (all 36 samples were
288 contaminated) followed by uangdong (78.18%) . As shown in Fig.3 and Table S10, all five
289 neonicotinoids were frequently detected in lychee, with ACE present at the highest frequency of
290 57.84%, followed by IMI at 27.45%. In comparison, the other three neonicotinoids, namely ACE, IMI,
291 THP, were present in longan at a rate of 55.56, 33.33 and 11.11%, respectively. In addition, ACE was
292 detected in all samples from uangxi province. The citrus honey with a neonicotinoid detection rate
293 of 67.65% was collected from Sichuan in the Southwestern region of China, Hubei in Central China
294 and Zhejiang in Eastern China. ACE, IMI and THM, which are employed to control *D. citri, Phyllocnistis*
295 *citrella* and aphids, exhibited the top 3 detection rates of 36.96, 34.78 and 17.39% in this survey (Fig.3).
296 The pesticide detection rate in rape honey was 49.68%, and IMI and ACE showed the top 2 rates of
297 42.16 and 36.27%, respectively, while the other three neonicotinoids were below 10%. The detection
298 rate of the five neonicotinoids in acacia and chaste honey was 43.36 and 23.08%, respectively. In
299 acacia honey, the detection rate of IMI and ACE was 52.27 and 27.73%, respectively, while the
300 detection rate of the other three neonicotinoids was close to or less than 10%. In comparison, in
301 chaste honey, the detection rate was highest for both IMI and THM at a rate of 27.78%, while that
302 for ACE was 22.21%. In jujube honey, neonicotinoids were detected at the average detection rate of
303 15.71%, and in all the contaminated samples only one neonicotinoids was detected, with IMI being
304 the most frequent. Also, we found IMI was detected in all honey species, while ACE was found in all
305 species except buckwheat, which also represented IMI and ACE were the most commonly used
306 neonicotinoids in China. Regarding the detected concentration in each floral of honey, except for
307 the average concentration of neonicotinoids in citrus honey and longan honey which was 14.67 and

13.38 μg/kg, respectively, the average concentration of neonicotinoids in other kinds of honey samples was below 10 μg/kg (Table S10). These results indicated the neonicotinoids in all floral of honey were at lower concentrations than the MRLs.

3.2.5. The difference of detection rates and concentrations of neonicotinoids in honey from commercial crops and non-commercial crops

The floral origins of honey was classified into two kinds, namely commercial crops and non-commercial crops, except for the wildflowers which have a complicated combination of different geographical area and different seasons. The neonicotinoids residues in commercial crops and non-commercial crops have been discussed with regard to detection rate, concentration and the main detected pesticides. Significant differences were found between commercial and non-commercial crops (X^2 =5.15, df=1, *P*=0.029, Table S12). Commercial crops in this study included 10 kinds of plants and 473 honey samples with a neonicotinoid detection rate of 45.45% at the average detected concentration of 6.79 μg/kg. Non-commercial crops included 5 crops and 149 samples with a neonicotinoid detection rate of 34.89% at the average detection concentration of 2.02 μg/kg. In addition, ACE and IMI showed the two highest detection rates of 42.81 and 35.78%, respectively, in all contaminated honey samples from commercial crops, while the other three neonicotinoids were present in the honey samples at less than 10%. In comparison, IMI, ACE, and THM showed the detection rate of 45.31, 23.44, and 15.63%, respectively, in all the contaminated honey samples from non-commercial crops, while the other two neonicotinoids were present in the honey samples at less than 10% (Table S13). The comparative analysis revealed that neonicotinoid pesticides are mainly detected in honey from commercial crops at a higher detection rate than that in honey from non-commercial crops. The most important reason for this difference is that the commercial crops are

330 intended to be sold for profit by farmers, so there is a high possibility that they have to be treated
331 with insecticides for pest prevention and control.
332 3.2.6. The difference of detection rates and concentrations of neonicotinoids in honey from
333 different entomological origins
334 *Apis mellifera* honey was higher than *Apis cerana* both in detection rate and detection
335 concentration of neonicotinoids. A total of 120 honey samples from *Apis cerana* were collected
336 from 5 provinces including ansu, uangdong, Hubei, Shaanxi, Sichuan with an average detection
337 rate of 32.50% at the concentration of 3.68 μg/kg. *Apis mellifera* honey samples were harvested
338 from 18 provinces and a total of 573 samples were collected with an average detection rate of
339 42.58% at the concentration of 6.09 μg/kg. Significant differences were found according to the
340 different entomological origins of honey (X^2=4.18, df = 1, P=0.042). Among all the contaminated
341 samples from *Apis cerana,* 79.49% of the samples contained one neonicotinoid, 20.51% of them
342 contained two or three neonicotinoids. As for *Apis mellifera* honey, 65.98% of the contaminated
343 samples contained one neonicotinoid, 32.79% of them (244 samples) contained two or three
344 neonicotinoids, and one sample contained four neonicotinoids. A total of 22 honey samples from
345 uangdong in Southern C hina, with the rate of 56.41% from *Apis cerana* were found to contain
346 neonicotinoid. For *Apis mellifera*, all samples from uangdong and uangxi in Southern China were
347 found to contain neonicotinoids, 70.59% of samples from Qinghai in Northwestern China also
348 contained neonicotinoids. *Apis cerana* honey origins included wildflowers, acacia, chaste, citrus,
349 jujube, rape, longan and lychee. The *Apis mellifera* honey included all 15 kinds of crops mentioned
350 above. Taking the wildflower and citrus as examples, the detection rate and detected
351 concentration in citrus were 28.57% and 0.38 μg/kg, respectively, in honey from *Apis cerana*. In

352 comparison, the detection rate and detected concentration were 90.48% and 17.68 μg/kg,
353 respectively, in honey from Apis mellifera. In addition, in A. cerana, the detection rate of ACE and
354 IMI was 48.98 and 22.45%, respectively, while that for THP and THM was the same at 10.20%, and
355 that of CLO was 8.16%. In comparison, in *A. mellifera,* the detection rate of ACE, IMI and THM was
356 38.75, 38.46, and 10.83%, respectively, while the other two neonicotinoids in all contaminated
357 honey samples were below 10%. Based on the above findings, it can be concluded that
358 neonicotinoid pesticides were detected at a higher rate and concentration in *Apis mellifera* honey
359 than those in *Apis cerana* honey. The most likely reason is that *Apis cerana* populations dwell in
360 mountains or high-elevation areas and consume nectar primarily from plants growing naturally on
361 the mountains, thus they would be less exposed to the pesticides.

362 **3.3. Dietary exposure risk assessment.**

363 In recent years, risk analysis has been widely applied to dietary exposure to pesticides residues
364 in food to provide a theoretical basis to guarantee the safety of agricultural products. Chronic
365 exposure, acute exposure and risk ranking are the most commonly used methods for risk
366 assessment calculation.[42] For chronic exposure risk assessment, median residue concentration of
367 each monitored pesticide is often used for chronic risk analysis[43], however, in our study, average
368 concentration rather than median concentration was applied to calculate long-term risk because it
369 was higher in most cases, and could assume a worst-case scenario[44]. Long-term exposure values
370 NEDI were notably lower than ADI values. Table 1 shows the %ADI values, the average of which was
371 9×10^{-4}, and IMI posed the highest chronic risk of the five evaluated neonicotinoids with a %ADI value
372 of 1.4×10^{-3}. The %ADI values of the five neonicotinoids were considerably less than 100, indicating
373 that the pesticide residues in honey from China exhibited a negligible exposure risk. Thus, exposure

374 to these five neonicotinoids via honey consumption is highly unlikely to cause harm to human health.

375 ARfD value is an important toxicological threshold, which was used to assess the health
376 damage caused by acute exposure to chemical pollutants. According to the World Health
377 Organization and JMPR database, the ARfD of the five neonicotinoid pesticides are set at 0.03-1
378 mg/kg. The acute exposure was calculated by maximum residue concentration of each pesticide and
379 maximum consumption of honey. The %ARfD values of these five pesticides were evaluated to be in
380 the range 1.3×10^{-3} – 2.4×10^{-1} and far less than 100, indicating that the acute risk of pesticide residues
381 is well within the acceptable range.

382 Despite long-term and short-term risk assessment showed negligible exposure risk posed by
383 honey consumption, the potential risk of the five neonicotinoids should be investigated due to
384 accumulation in organisms. The risk scores of these five pesticides were calculated and are shown
385 in Table 3. According to the results, ACE and IMI had a medium risk with the score of 15.71 and 15.64,
386 respectively, which did not exhibit chronic risk or acute risk. The scores of the other pesticides were
387 lower than 15, resulting in a low risk. These results showed that the risk score is not always in line
388 with the chronic risk and acute risk, implying that the risk of a pesticide is the combination of all
389 factors. Simultaneously, more attention should be paid to risk assessment, particularly for ACE and
390 IMI, due to their high usage and higher risk scores.

391 **3.4. Risks to bees.**

392 The impacts of dietary exposure of bees to neonicotinoids have been extensively
393 investigated.[45-47] Concentrations of IMI, THM and CLO above 1 μg/kg have been found to have a
394 range of sublethal impacts on diverse aspects of honey bee biology[48, 49], including impaired
395 immune response, reduced fecundity of queens, lowered homing success, and impaired learning,

all of which will reduce the long-term health and fitness of bee colonies. Where detected, IMI, THM and CLO were present at mean concentrations of 5.01, 1.75 and 4.36 μg/kg in our honey samples, respectively, well within the range likely to reduce colony health[5, 7, 9, 505, 7, 9, 525, 7, 9, 525, 7, 9, 505, 7, 9, 495, 7, 9, 47,5, 7, 9, 47]. Although ACE was the most frequent contaminant on honey in our study, exposure to ACE (and to the related compound THP) is less likely to be impacting on colonies as these two compounds are considerable less toxic to honey bees in acute toxicity tests[45].

In conclusion, an extensive survey of the presence of neonicotinoid pesticides in honeys from across China revealed that the honeys from lychee, longan, citrus, rape and acacia had the higher detection rate of neonicotinoid pesticides. In general, the detection rate and concentration of neonicotinoid pesticides in honey from commercial crops was higher than those in honey from non-commercial crops. Also, honey from south China had higher detection rates and concentrations of neonicotinoid pesticides than honey from areas in north China. Honey from *Apis mellifera* had higher detection rate and concentration of neonicotinoid pesticides than that from *Apis cerana*. ACE and IMI were the most frequently detected and, based on the ranking of residual risk, presented a medium risk for consumers. However, the five neonicotinoid pesticides represented no risk in chronic dietary intake risk and acute dietary intake risk. Thus, taken together, the results of both risk ranking and dietary intake risk, indicate that the detected residues of neonicotinoids in honey are unlikely to be harmful to human health. However, two or more neonicotinoids were often found concurrently, and cumulative risks and possibly synergisms are not understood and need further study. Concentrations of neonicotinoids found in honey were sufficient to pose a significant threat to the health of the bees.

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549 **Figure Captions:**
550 Figure 1: IS map showing the loca tions information of honey samples in China, and the average
551 concentration of total neonicotinoid pesticides in every province of China (The grey areas
552 represented no sample from these provinces.).
553 Figure 2: The detection rate and concentration of the five neonicotinoid pesticides evaluated. A: The
554 detection rate of samples with 0, 1, 2, 3, 4 and 5 individual neonicotinoids. B: The detection rate of
555 five neonicotinoids in all samples and the proportion of detection concentration in five individual
556 neonicotinoids. C: The average detection concentration of the five neonicotinoid pesticides.
557 Figure 3: The detection rate of five neonicotinoid pesticides in each of the plant species. A: Lychee
558 honey; B: Longan honey; C: Citrus honey; D: Rape honey; E: Chaste honey; F: Wildflower honey; :
559 Linden honey; H: Acacia honey; I: Jujube honey.
560 Figure 4: The proportion of samples with 0, 1, 2, 3 and 4 individual neonicotinoids of five

neonicotinoid pesticides in each of the plant species. A: Lychee honey; B: Longan honey; C: Citrus honey; D: Rape honey; E: Chaste honey; F: Wildflower honey; : Linden honey; H: Acacia honey; I: Jujube honey.

Table Captions:

Table 1: Chronic risks, acute risks and risk scores of five neonicotinoids in honey consumption

566 Table 1 Chronic risks, acute risks and risk scores of five neonicotinoids in honey consumption

Pesticide	Chronic risk assessment				Acute risk assessment				Risk score
	ADI (mg/kg)	Average residue (mg/kg)	NEDI (mg/kg • d)	%ADI (%)	Maximum residue (mg/kg)	ARfD (mg/kg)	ESTI (mg/kg)	%ARfD (%)	
ACE	7.00E-02	4.66E-03	7.76E-07	1.10E-03	1.47E-01	1.00E-01	2.44 E-04	2.45E-01	15.71
CLO	1.00E-01	4.36E-03	7.27E-07	7.00E-04	3.44E-02	6.00E-01	5.73 E-05	9.60E-03	8.05
IMI	6.00E-02	4.91E-03	8.18E-07	1.40E-03	8.86E-02	4.00E-01	1.48 E-04	3.69E-02	15.64
THP	1.00E-02	4.80E-04	7.93E-08	8.00E-04	1.91E-03	3.00E-02	3.18E-06	1.06E-02	12.14
THM	8.00E-02	1.63E-03	2.72E-07	3.00E-04	7.95E-03	1.00E+00	1.33 E-05	1.30E-03	12.19

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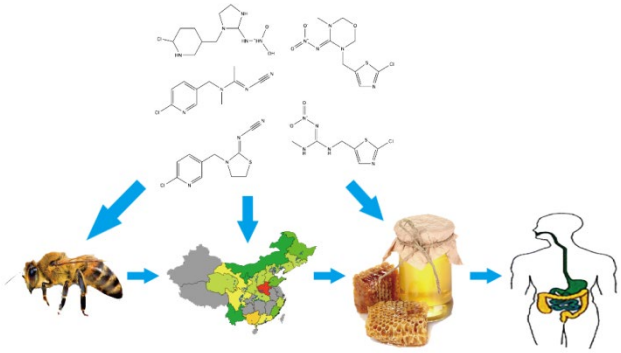

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576 **TOC graphic**